EM 199907
EW 19990705

L10 ANSWER 18 OF 41 MEDLINE
AN 97146199 MEDLINE
DN 97146199
TI Treatment of hypercholesterolemia in patients undergoing multiple coronary angioplasties.
AU Marques V; Bowser S; Hendrickxs J; Ruffner R
CS Dept. of Medicine, Shadyside Hospital, Pittsburgh, Pennsylvania 15232, USA.
SO REVISTA PORTUGUESA DE CARDIOLOGIA, (1996 Nov) 15 (11) 787-91, 771-2. Journal code: AOW. ISSN: 0304-4750.
CY Portugal
DT Journal; Article; (JOURNAL ARTICLE)
LA English
EM 199704
EW 19970403

L10 ANSWER 21 OF 41 MEDLINE
AN 96403003 MEDLINE
DN 96403003
TI Prevention of restenosis after coronary angioplasty with low-density lipoprotein apheresis.
AU Adachi H; Niwa A; Shinoda T
CS Department of Medicine, Musashino Red Cross Hospital, Tokyo, Japan.
SO ARTIFICIAL ORGANS, (1995 Dec) 19 (12) 1243-7. Journal code: 8ZK. ISSN: 0160-564X.
CY United States
DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199702
EW 19970204

L10 ANSWER 11 OF 41 MEDLINE
AN 1998076997 MEDLINE
DN 98076997
TI Adenovirus gene therapy for ***hypercholesterolemia*** , thrombosis and ***restenosis*** .
AU Gerard R D; Collen D
CS Center For Transgene Technology and Gene Therapy, Flanders Interuniversity Institute for Biotechnology, Katholieke Universiteit Leuven, Belgium.
SO CARDIOVASCULAR RESEARCH, (1997 Sep) 35 (3) 451-8. Ref: 69
Journal code: COR. ISSN: 0008-6363.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199803

L10 ANSWER 31 OF 41 MEDLINE
AN 95005582 MEDLINE
DN 95005582
TI Comparison of three porcine ***restenosis*** models: the relative importance of ***hypercholesterolemia*** , endothelial abrasion, and stenting.

ADONIS - Electronic Journal Services

Requested by

Adonis

Article title	Prevention of restenosis after coronary angioplasty with low-density lipoprotein apheresis
Article identifier	0160564X96000090
Authors	Adachi_H Niwa_A Shinoda_T
Journal title	Artificial Organs
ISSN	0160-564X
Publisher	Blackwell USA
Year of publication	1995
Volume	19
Issue	12
Supplement	0
Page range	1243-1247
Number of pages	5
User name	Adonis
Cost centre	Development
PCC	$12.00
Date and time	Friday, December 29, 2000 3:23:21 PM

Copyright © 1991-1999 ADONIS and/or licensors.

The use of this system and its contents is restricted to the terms and conditions laid down in the Journal Delivery and User Agreement. Whilst the information contained on each CD-ROM has been obtained from sources believed to be reliable, no liability shall attach to ADONIS or the publisher in respect of any of its contents or in respect of any use of the system.

18069302

Artificial Organs
19(12):1243–1247. Blackwell Science, Inc., Boston
© 1995 International Society for Artificial Organs

Prevention of Restenosis after Coronary Angioplasty with Low-Density Lipoprotein Apheresis

Hiromasa Adachi, Akihiro Niwa and *Toshio Shinoda

*Department of Medicine, Divisions of Cardiology and *Nephrology, Musashino Red Cross Hospital, Musashino City, Tokyo, Japan*

Abstract: A prospective study was performed to determine whether low-density lipoprotein (LDL) apheresis, when performed only immediately before and after percutaneous transluminal coronary angioplasty (PTCA), is effective in preventing restenosis of coronary artery lesions following PTCA. Thirty-six patients with coronary heart disease (CHD) and hypercholesterolemia were divided into 2 groups. The 9 patients in the LDL group underwent LDL-apheresis 1 day before and 5 days after PTCA while the 27 patients of the control group underwent PTCA but did not undergo LDL-apheresis. Follow-up coronary angiography (CAG) was performed 4 months after PTCA. The rate of restenosis of coronary artery lesions was significantly lower in the LDL group (0%) than in the control group (30%). These findings suggest that LDL-apheresis, when performed before and after PTCA, is effective in preventing restenosis of coronary artery lesions in patients with CHD and hypercholesterolemia. **Key Words:** Low-density lipoprotein apheresis—Restenosis of coronary artery lesions—Percutaneous transluminal coronary angioplasty—Coronary heart disease—Hypercholesterolemia.

The role of percutaneous transluminal coronary angioplasty (PTCA) (1) in the treatment of coronary heart disease (CHD) has been well-established. However, restenosis of dilated lesions frequently occurs at a high rate of frequency (30–40%) within several months of PTCA (2–5). Low-density lipoprotein (LDL) apheresis, a new technique of therapeutic plasmapheresis for removal of LDL (6), has been reported to be effective in the treatment of patients with CHD and familial hypercholesterolemia by virtue of preventing restenosis of dilated lesions following PTCA (7) and stenosis of coronary artery bypass grafts (CABG) (8). It accomplishes this by reducing the serum LDL-cholesterol and/or lipoprotein (a) (Lp[a]) when it is performed intermittently throughout the follow-up period after PTCA or CABG. We attempted to determine whether LDL-apheresis, when performed immediately before and after PTCA, can prevent restenosis of coronary artery lesions in patients with CHD and hypercholesterolemia in whom the serum cholesterol levels are not as high as that in patients with familial hypercholesterolemia.

Received March 1995.
Address correspondence and reprint requests to Dr. Toshio Shinoda at the Department of Medicine, Division of Nephrology, Musashino Red Cross Hospital, 1-26-1 Kyonan-cho, Musashino City, Tokyo 180, Japan.

PATIENTS AND METHODS

Thirty-six patients with CHD and hypercholesterolemia were enrolled in the present study. The patients were candidates for elective PTCA whose coronary artery lesions had been assessed by coronary angioplasty (CAG) and who had been judged to have the potential for successful treatment with PTCA. They had serum cholesterol levels of 220 mg/dl or higher and had been treated with drugs such as pravastatin. They had also been treated with calcium antagonists and/or nitrates. These medications were continued throughout the study.

The patients were divided into 2 groups, an LDL group and a control group. After being informed of the details of the study, a total of 9 patients (5 men and 4 women) agreed to undergo LDL-apheresis before and after PTCA (LDL group). The LDL group included 5 patients with old myocardial infarction and 4 patients with angina pectoris (Table 1). Thirteen coronary artery lesions were observed in these 9 patients. The remaining 27 patients (23 men and 4 women) did not agree to undergo LDL-

TABLE 1. *Patients' characteristics*

	LDL group	Control group
Number of patients (male/female)	9 (5/4)	27 (23/4)
Age (years)	62 ± 8.9	60 ± 10.5
Disease		
Angina pectoris	4	17
Old myocardial infarction	5	10
Number of coronary lesions	13 (10)[a]	48 (33)[a]
Left anterior descending branch	4 (2)	20 (16)
Left circumflex branch	3 (2)	13 (8)
Right coronary artery	6 (6)	15 (9)

[a] Number of coronary lesions that were dilated by PTCA.

apheresis (control group). The control group included 10 patients with old myocardial infarction and 17 patients with angina pectoris (Table 1). There were a total of 48 coronary artery lesions in these 27 patients. There was no difference in age, gender, number, or degree of coronary artery lesions or serum lipid levels between the LDL and control groups (Tables 1 and 2, Fig. 1).

The serum total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL-cholesterol, triglyceride, apoprotein (Apo) A-I, Apo B, the Apo B/A-I ratio, and Lp(a) were determined before PTCA and at the follow-up CAG. They were also determined before and after LDL-apheresis in the LDL group. Total cholesterol and triglyceride levels were measured with an autoanalyzer (Automatic Analyzer 736-40, Hitachi, Tokyo, Japan) and HDL-cholesterol with another autoanalyzer (COBAS MIRA PLUS, Roche Japan, Tokyo, Japan). LDL-cholesterol was calculated using Friedwald's equation. The apoproteins were measured by turbidimetric immunoassay and Lp(a) by enzyme-linked immunosorbent assay.

LDL-apheresis was performed 1 day before and 5 days after PTCA using a plasma separator, the Sulfrax FS-05 (Kaneka, Osaka, Japan), an adsorbent column for LDL (Liposorba LA-15, Kaneka) and an operating system, MA-01 (Kaneka). The cubital veins were used bilaterally for vascular access. The forearms were warmed with warming pads to obtain a rate of blood flow of 70–80 ml/min. Separated plasma was processed with the LA-15 column at a

TABLE 2. *Degree of coronary artery stenosis*

Group	Before PTCA (%)	Just after PTCA (%)	Follow-up CAG (%)
LDL	88.7 ± 9.6	36.5 ± 9.9	41.0 ± 12.9
Control	89.6 ± 6.5	38.4 ± 15.8	53.5 ± 26.9

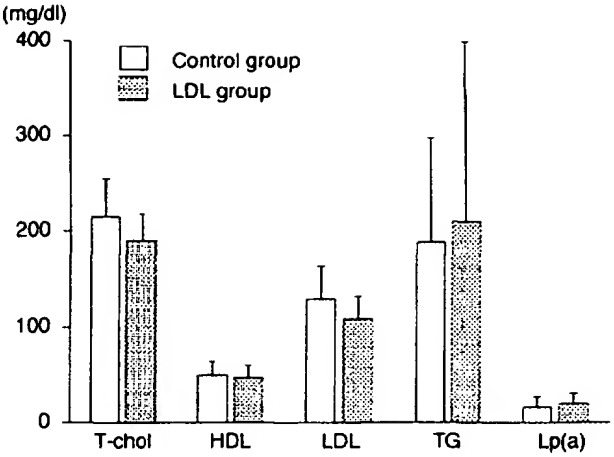

FIG. 1. *Serum lipid levels in the control and LDL groups are shown. Values are mean ± SD. T-chol, total cholesterol; HDL, HDL-cholesterol; LDL, LDL-cholesterol; TG, triglyceride; Lp(a), lipoprotein (a).*

rate of 35 ml/kg of body weight (BW) or higher in a session of 120–180 min.

The degree of coronary artery stenosis was determined by densitometry using the Cardio 500 (Kontron, München, Germany). A follow-up CAG was performed 4 months after PTCA. The coronary artery lesions seen in the CAG immediately after PTCA and the follow-up CAG were compared with respect to location, number, and degree of stenosis. On the follow-up CAG, restenosis was defined as recurrent loss of 50% or more of the luminal diameter in the dilated coronary arteries.

Statistical analyses were performed using the Student's *t*-test for continuous variables, Wilcoxon's signed-ranks test for Lp(a), and the chi-square test for comparisons of frequency of gender or restenosis between the two groups; p values less than 0.05 were considered statistically significant.

RESULTS

PTCA was performed for 10 of the 13 lesions in the LDL group and for 33 of the 48 lesions in the control group. The degree of coronary artery stenosis was improved by PTCA from 88.7 ± 9.6% to 36.5 ± 9.9% in the LDL group; and from 89.6 ± 6.5% to 38.4 ± 15.8% in the control group. There

TABLE 3. *Rate of restenosis at follow-up CAG*

Group	Number of segments restenosis/dilated	Rate of restenosis (%)
LDL	0/10	0[a]
Control	10/33	30[a]

[a] $p < 0.05$.

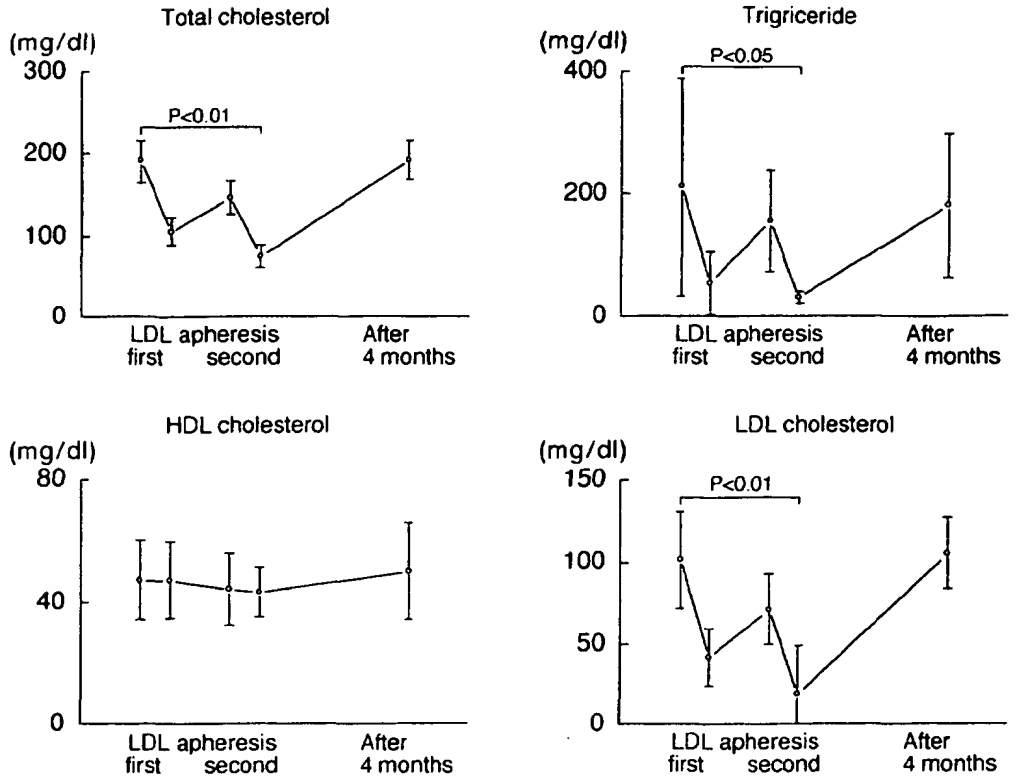

FIG. 2. The changes in serum lipid levels and the time-course of treatment in the LDL group patients (1) are shown. Values are mean ± SD.

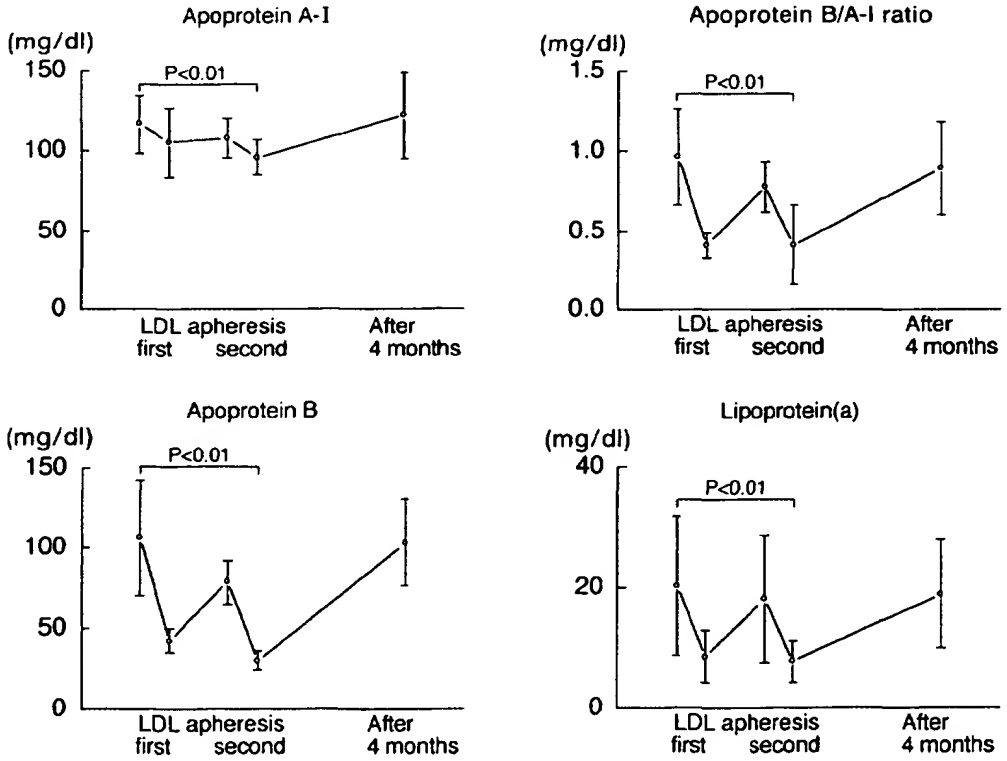

FIG. 3. The changes in the serum lipid levels and the time-course of treatment in the LDL group patients (2) are shown. Values are mean ± SD.

18069302

was no difference in the degree of coronary artery stenosis immediately after PTCA between the two groups (Table 2).

On follow-up CAG, the mean degree of coronary artery stenosis was slightly lower in the LDL group (41.0 ± 12.9%) than in the control group (53.5 ± 26.9%; Table 2). Restenosis of PTCA-dilated lesions was not observed in the LDL group (0%) but was observed in 10 of 33 lesions (30%) in the control group (Table 3; $p < 0.05$).

In the LDL group, serum cholesterol was decreased from 190.2 ± 26.2 to 104.8 ± 16.6 mg/dl by the first session of LDL-apheresis (1 day before PTCA) and from 145.8 ± 20.2 to 75.3 ± 14.1 mg/dl by the second session (5 days after PTCA) (Fig. 2). By 4 months after PTCA, serum cholesterol (191.3 ± 24.0 mg/dl) had returned nearly to the level present before the first LDL apheresis in the LDL group. The same trend was observed for other parameters of lipid metabolism including serum triglyceride, HDL-cholesterol, LDL-cholesterol, Apo A-I, Apo B, the Apo B/A-I ratio, and Lp(a) in the LDL group (Figs. 2 and 3).

DISCUSSION

The rate of restenosis after PTCA was significantly lower in the LDL group than in the control group. In addition, the degree of stenosis of PTCA-dilated lesions at follow-up CAG was slightly lower in the LDL group than in the control group. The rate of 30% in the control group is almost the same as that noted in previous reports (2–5). These findings suggest that LDL-apheresis, when performed immediately before and after PTCA, decreases the restenosis that occurs following PTCA in patients with CHD and hypercholesterolemia.

Prevention of restenosis after PTCA by LDL-apheresis performed in the same manner as in the present study was reported in a recent study (9). In that study, the rate of restenosis was not improved by LDL-apheresis for the entire group of patients who underwent LDL-apheresis but only in a subgroup of 42 patients whose Lp(a) levels were reduced by 50% or more by LDL-apheresis. The authors emphasized the importance of the role played by Lp(a) in the initiation of restenosis after PTCA. They suggested several mechanisms that might cause restenosis, including suppression of fibrinolytic activity, thrombus formation and the subsequent release of growth factors, promotion of vascular smooth muscle growth, and an increase of extracellular matrix. In the present study, prevention of restenosis of PTCA-dilated lesions was observed in patients who underwent LDL-apheresis irrespective of their LP(a) levels.

On the other hand, in another study (10) no association was found between Lp(a) and the frequency of restenosis after PTCA despite the presence of a strong association between Lp(a) and coronary artery disease. They observed an association between restenosis after PTCA and a low serum HDL_2 or high Apo B level. In addition, other authors suggested that the short-term reduction of cholesterol increased the coronary arterial/arteriolar flow capacity (11). The beneficial effects of cholesterol-lowering therapy on coronary endothelium-dependent relaxation have also been reported (12).

In the present study, no difference was found in the parameters of lipid metabolism between the LDL and control groups. In addition, no difference was observed in the serum cholesterol level between the 2 groups at follow-up CAG. The serum cholesterol, LDL-cholesterol, Apo B, and Lp(a) levels were markedly decreased following 2 sessions of LDL-apheresis. However, this effect was only transient with the use of our protocol. LDL-apheresis had little effect on HDL-cholesterol and Apo A-I. In the LDL group, the time-averaged levels of serum cholesterol and Lp(a) were about 125 and 13 mg/dl, respectively, during the week on the second day of which PTCA was performed.

Thus, the transient decrease in serum cholesterol and/or Lp(a) was responsible for the prevention of restenosis of PTCA-dilated coronary lesions by LDL-apheresis. Deposition of cholesterol in vascular walls is one of the most important mechanisms in the initiation and progression of atherosclerotic lesions. In the case of PTCA, endothelial injury might play a role in triggering subsequent restenosis. Very low levels of serum cholesterol might lessen deposition of cholesterol in the injuried vascular walls after PTCA.

REFERENCES

1. Gruentzig AR. Transluminal dilation of coronary artery stenosis. *Lancet* 1978;1:263.
2. Fanelli C, Aronoff R. Restenosis following coronary angioplasty. *Am Heart J* 1990;119:357–68.
3. Holmers DR Jr, Vlietstra RE, Smith CH, Vetrovec GW, Kent KM, Cowley MJ, Faxon DP, Gruentzig AR, Kelsey SF, Detre KM, van Randen JM, Mock MB. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): A report from the PTCA Registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol* 1984;53:77c–81c.
4. Leimgruber PP, Roubin GS, Hollman J, Cotsonis GA, Meier B, Douglas JS, King SB III, Gruentzig AR. Restenosis after successful coronary angioplasty in patients with single-vessel disease. *Circulation* 1986;73:710–7.
5. Guiteras Val P, Bourassa MG, David PR, Bonan R, Crepeau J, Dyrda I, Lesperance J. Restenosis after successful percu-

18069302

taneous transluminal coronary angioplasty: The Montreal Heart Institute experience. *Am J Cardiol* 1987;60:50–8.
6. Gordon BR, Kelsey SF, Bilheimer DW, Brown DC, Dau PC, Gotto AM Jr, Illingworth R, Jones PH, Leitman SF, Prihoda JS, Stein EA, Stern TN, Zavoral JH, Zwiener RJ, for the Liposorber Study Group. Treatment of refractory familial hypercholesterolemia by low-density lipoprotein apheresis using an automated dextran sulfate cellulose adsorption system. *Am J Cardiol* 1992;70:1010–6.
7. Kanemitsu S, Tekekoshi N, Murakami E. Effects of LDL apheresis on restenosis after angioplasty. *Chem Phys Lipids* 1994;67/68:339–43.
8. Takahashi T, Nakano S, Shimazaki Y, Kaneko M, Hirata N, Nakamura T, Matsuzawa Y, Kitamura S, Matsuda H. Long-term appraisal of coronary bypass operations in familial hypercholesterolemia. *Ann Thorac Surg* 1993;56:499–505.
9. Daida H, Lee YJ, Yokoi H, Kanoh T, Ishiwata S, Kato K, Nishikawa H, Takatsu F, Kato H, Kutsumi Y, Yamada N, Noma A, Yamaguchi H, and the Low-Density Lipoprotein Apheresis Angioplasty Restenosis Trial (L-ART) Group. Prevention of restenosis after percutaneous transluminal coronary angioplasty by reducing lipoprotein (a) levels with low-density lipoprotein apheresis. *Am J Cardiol* 1994;73:1037–40.
10. Cook T, Sheahan R, Foley D, Reilly M, D'Arcy G, Jauch W, Gibney M, Gearty G, Crean P, Walsh M. Lipoprotein(a) in restenosis after percutaneous transluminal coronary angioplasty and coronary artery disease. *Circulation* 1994;89:1593–8.
11. Gould KL, Martucci JP, Goldberg DI, Hess MJ, Edens RP, Latifi R, Dudrick SJ. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease, a potential noninvasive marker of healing coronary endothelium. *Circulation* 1994;89:1530–8.
12. Leung W-L, Lau C-P, Wong C-K. Beneficial effects of cholesterol-lowering therapy on coronary endothelium-dependent relaxation in hypercholesterolemic patients. *Lancet* 1993;341:1496–500.